AHRQ Comparative Effectiveness Review Surveillance Program

CER # 35:

Comparative Effectiveness of Terbutaline Pump for the Prevention of Preterm Birth

Original release date:
September, 2011

Surveillance Report (1st Assessment/cycle 1):
May, 2012

Surveillance Report (2nd Assessment/cycle 2):
December, 2012

Key Findings (1st Assessment/cycle1):

- KQ1-KQ6 are up-to-date
- Expert opinion: Both experts stated that the conclusions for KQ1 – KQ6 were still valid
- No new saftey alerts

Key Findings (Cumulative: 1st and 2nd assessment/cycle 1-2)

Unchanged from the 1st assessment:

- KQ1-KQ6 are up-to-date
- Expert opinion: Both experts stated that the conclusions for KQ1 – KQ6 were still valid
- No new saftey alerts

Summary Decision:

This CER's priority for updating is **LOW**

Authors:

Investigators: Nadera Ahmadzai, Becky Skidmore
Technical support: Raymond Daniel, Sophia Tsouros
Advisory panel: David Moher, Mohammed Ansari
Oversight/supervision: David Moher, Chantelle Garritty

None of the investigators has any affiliation or financial involvement that conflicts with material presented in this report.

Acknowledgments

The authors gratefully acknowledge clinical content experts Dr. Jeff Andrews and James Reichmann for their contributions to this project.

Subject Matter Experts

Jeff Andrews, M.D., F.R.C.S.C., F.A.C.O.G.
Associate Professor,
Vanderbilt University Medical Center
Nashville, TN

James Reichmann, M.B.A.
American Homepatient Inc.
Brentwood, TN

Contents

Tables

Appendices

1. Introduction

The purpose of this mini-report was to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether or not the CER No. 35 (Comparative Effectiveness of Terbutaline Pump for the Prevention of Preterm Birth) is in need of updating. This CER was originally released in September, 2011. The first surveillance assessment report of this CER was due for a surveillance assessment in 6 months of its release, and it was submitted to AHRQ in May, 2012. This second assessment was completed in December 2012.

This CER included 14 publications identified by using searches through April 1st , 2011 and addressed six key questions to evaluates the level of evidence currently available to support the effectiveness and safety of using Terbutaline Pump for the Prevention of Preterm Birth. The objectives of this review were to examine the efficacy, effectiveness, and safety of the SQ terbutaline pump as prolonged maintenance tocolysis for inhibiting progression of parturition in women with arrested acute preterm labor. These objectives were framed in the following Key Questions:
In women with arrested preterm labor, does treatment with an SQ infusion of terbutaline delivered by a pump, in comparison with placebo, conservative treatment, or other interventions:

Key Question 1: improve neonatal health outcomes, including bronchopulmonary dysplasia, neonatal death, death within initial hospitalization, significant intraventricular hemorrhage (grade III/IV), necrotizing enterocolitis, periventricular leukomalacia, retinopathy of prematurity, seizures, sepsis, and stillbirth for the following subgroups:

a. Women <28 weeks of gestation (extremely preterm)?
b. Women between 28 weeks and 31 weeks of gestation (very preterm)?
c. Women between 32 weeks and 33 weeks of gestation (preterm)?
d. Women between 34 weeks and 36 weeks of gestation (later preterm)?
e. Multiple gestations?
f. Racial or ethnic subgroups?
g. Women with previous preterm birth?
h. Women with history of preeclampsia?
i. Women with RPTL and women without RPTL?

Key Question 2: improve other surrogate outcomes, including gestational age at delivery, incidence of delivery at various gestational ages (<28 weeks, < 32 weeks, <34 weeks, <37 weeks), mean prolongation of pregnancy (days), birth weight, ratio of birth weight/gestational age at delivery, pregnancy prolongation index, need for assisted ventilation, need for oxygen per nasal cannula, and neonatal intensive care unit (NICU) admission for the following subgroups:

a. Women <28 weeks of gestation (extremely preterm)?
b. Women between 28 weeks and 31 weeks of gestation (very preterm)?
c. Women between 32 weeks and 33 weeks of gestation (preterm)?
d. Women between 34 weeks and 36 weeks of gestation (later preterm)?
e. Multiple gestations?
f. Racial or ethnic subgroups?
g. Women with previous preterm birth?
h. Women with history of preeclampsia?

i. Women with RPTL and women without RPTL?

Key Question 3: increase the maternal harms of arrhythmia, heart failure, hyperglycemia, hypokalemia, maternal mortality, myocardial infarction, pulmonary edema, or refractory hypotension, or result in an increased rate of maternal discontinuation of therapy or maternal withdrawal due to adverse effects (Withdrawal- AE)?

Key Question 4: increase the neonatal terbutaline-related harms of hypoglycemia, hypocalcemia, and ileus?

Key Question 5: Can the differences in the outcomes above be partially explained by the differences in level of care (e.g., frequency of followup, nurse visits, concomitant treatment, etc.) and level of activity (e.g., other children in the home, marital/support status, working status, bedrest, etc.) between the terbutaline pump group and the comparator group?

Key Question 6: What is the incidence of failure of the pump device used for terbutaline infusion, including missed doses, dislodgment, and overdose?

The conclusion(s) for each key question are found in the executive summary of the CER report.[1]

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The Food and Drug Administration (FDA) surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, saftey surveillance alerts), a consensus-based conclusion was drawn whether or not any given conclusion warrants any updating (up to date, possibly out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere. [2-4]

2.1 Literature Searches

Cycle 2 (2nd assessment)

The same search strategy was used as in the 1st assessment (cycle 1) but using different search dates for MEDLINE (Oct 1, 2010 to Nov 9, 2012), EMBASE (2011 Week 1 to 2012 Week 44), Cochrane Library (2011-2012), CINAHL (Published from: September 1st 2011 to November 9 2012), and Centre for Reviews and Dissemination (University of York, UK) 30/09/2011 to 09/11/2012 as per the original search strategies appearing in the CER's Appendix A.[1] Restricting by journal title was not possible in the Cochrane Library, Cinahl or CRD searches and pertinent citations were instead selected from the results.

Cycle 1 (1st assessment)

The CER search strategies were reconstructed in Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), Embase, and EBM Reviews - Cochrane Central Register of Controlled Trials using the OVID platform, Centre for Reviews and Dissemination (University of York, UK), and in CINAHL using the EBSCOhost platform as per the original search strategies appearing in the CER's Appendix A. Searches were limited to 2010 to present (March 30th, 2012). The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were applied according to the databases indicated in the appendix and in the search strategy section of the CER report. The MEDLINE and Embase searches were limited to five general medical journals (Annals of Internal Medicine; BMJ; JAMA; Lancet; and New England Journal of Medicine) and five specialty journals (Am J Obstet Gynecol, Am J Perinatol, Int J Gynaecol Obstet, Obstet Gynecol, BJOG). Restricting by journal title was not

possible in the EBM, Cinahl or CRD searches and pertinent citations were instead selected from the results. Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

The identified bibliographic record was screened using the same inclusion/exclusion criteria as one described in the original CER.[1]

2.3 Expert Opinion

Cycle 2 (2nd assessment)

We contacted the 2 experts that had responded to the first assessment and requested them to provide their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

Cycle 1 (1st assessment)

In total, 10 experts (5 experts who served as part of the technical expert panel and 5 who served as peer reviewers of the original report) were requested to provide their feedback in a provided their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER would examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only. For any given CER that included a meta-analysis, the assessment started with the identification of qualitative signal(s), and if no qualitative signal was found, this assessment extended to identify any quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The definition and categories of updating signals are presented in Appendix B and publications. [2-4]

2.5 Compilation of Findings and Conclusions

All the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and saftey surveillance alerts) was collated and summarized. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, and saftey surveillance alerts) presented in a tabular form, a conclusion was drawn whether or not any conclusion(s) of the CER warrant(s) updating.

Conclusions were drawn based on four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating
- Original conclusion is **out of date** and this portion of CER is in need of updating

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from saftey, etc.

2.6 Determining Priority for Updating

Determination of priority groups (i.e., Low, Medium, and High) for updating any given CER was based on two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?
- How out of date are the conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

Cycle 2 (2nd assessment)

A total of 3 bibliographic records were identified: MEDLINE=0, EMBASE=3, Cochrane Library =0 (including Database of Systematic Reviews, Database Abstracts of Reviews of Effects, and Health Technology Assessments), Cinahl=0, and Centre for Reviews and Dissemination=0. After de-duping, the same 3 records remained of which 2[5,6] records were excluded at the abstract and title screening because they were not on the intervention of interest, and 1[7] was excluded at the full text screening because it was among the excluded articles in the original CER. Thus, no publication was included in the report.

Cycle 1 (1st assessment)

A total of 5 bibliographic records were identified. After de-duping, 1 record remained and deemed potentially eligible for full text screening. After full text screening this record did not meet the eligibility criteria.[8] Thus, no publication was included in the report.

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

Cumulative cycles: 1 and 2 (1st and 2nd assessments)

No eligible study was identified and included in this report.

3.2.2 Qualitative signals

Cumulative cycles: 1 and 2 (1st and 2nd assessments)

Identification of qualitative signals was not applicable because no new study was identified through the update search.

Key question #1 -6

The conclusions from Key question 1 to 6 are still valid. **No Signal**

3.2.3 Quantitative signals

Cumulative cycles: 1 and 2 (1st and 2nd assessments)

Identification of qualitative signals was not applicable because no new study was identified through the update search.

3.3 Saftey surveillance alerts

No new saftey alerts was identified.

3.4 Expert opinion

Cycle 2 (2nd assessment)

Both contacted clinical experts provided their responses/feedback in the matrix table (Appendix D). Both experts stated that the conclusions outlined in the executive summary of the CER were still valid. They were not aware of any additional publications that could invalidate the conclusions.

Cycle 1 (1st assessment)

Two of the 10 contacted clinical experts provided their responses/feedback in the matrix table (Appendix D). Both experts stated that the conclusions outlined in the executive summary of the CER were still valid. They were not aware of any additional publications that could invalidate the conclusions.

4. Conclusion

Summary results and conclusions according to the information collated from different sources (update search, saftey surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the two assessments (cycles 1-2), this CER is categorized in **Low** (unchanged from the 1st assessment) priority group for updating.

Key Question # 1- Key Question # 6

Cumulative cycles: 1 and 2 (1st and 2nd assessments)

Signals from studies identified through update search: i) No signal was detected because no new study was identified through the update search. **No Signal**

Experts: Both experts stated that conclusions in the key question # 1-6 were still valid.

Saftey surveillance alerts: No new alert was identified.

Conclusion: **All conclusions are still valid**

Summary Table (Terbutaline)

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		FDA/ Health Canada surveillance alerts	Expert opinion (CER + local)	Validity of CER conclusion(s)	
		Qualitative	Quantitative			Cycle 1 Assessment	Cycle 1-2 (Total cumulative assessment)
Key Question 1: improve neonatal health outcomes, including bronchopulmonary dysplasia, neonatal death, death within initial hospitalization, significant intraventricular hemorrhage (grade III/IV), necrotizing enterocolitis, periventricular leukomalacia, retinopathy of prematurity, seizures, sepsis, and stillbirth for the following subgroups: a. Women <28 weeks of gestation (extremely preterm)? b. Women between 28 weeks and 31 weeks of gestation (very preterm)? c. Women between 32 weeks and 33 weeks of gestation (preterm)? d. Women between 34 weeks and 36 weeks of gestation (later preterm)? e. Multiple gestations? f. Racial or ethnic subgroups? g. Women with previous preterm birth? h. Women with history of preeclampsia? i. Women with RPTL and women without RPTL?							
Strength of evidence is insufficient for bronchopulmonary dysplasia, death within initial hospitalization, and significant intraventricular hemorrhage (grade III/IV). Based on one retrospective cohort of medium risk of bias, the strength of evidence favoring the SQ terbutaline pump compared with oral tocolytics for	**Cycle 2 (December 2012)**					**Up-to-date**	**Up-to-date**
	No new eligible evidence was identifie d	**None**	**None**	No new safety alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence		

gestation and RPTL is low (Table B). This study investigated women from the Matria database and reported a statistically significant difference in neonatal death in favor of SQ terbutaline pump (OR = 0.09, 95% CI: 0.01, 0.70).19 Sparse evidence from underpowered studies addressed necrotizing enterocolitis, retinopathy of prematurity, and sepsis with inconclusive results.11,13 No data were available for periventricular leukomalacia and seizures. Three retrospective cohort studies from the Matria database reported stillbirths in women with RPTL and single or twin gestation.17-19 All three studies found nonsignificant differences between the SQ terbutaline pump and oral tocolytics. However, these studies were likely underpowered to detect a difference in still birth, given the small number of events (<1%).					invalidate the findings.		
	Cycle 1 (May 2012)						
	No new eligible evidence was identified	**None**	**None**	No new safety alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		
Key Question 2: improve other surrogate outcomes, including gestational age at delivery, incidence of delivery at various gestational ages (<28 weeks, < 32 weeks, <34 weeks, <37 weeks), mean prolongation of pregnancy (days), birth weight, ratio of birth weight/gestational age at delivery, pregnancy prolongation index, need for assisted ventilation, need for oxygen per nasal cannula, and neonatal intensive care unit (NICU) admission for the following subgroups: a. Women <28 weeks of gestation (extremely preterm)? b. Women between 28 weeks and 31 weeks of gestation (very preterm)? c. Women between 32 weeks and 33 weeks of gestation (preterm)? d. Women between 34 weeks and 36 weeks of gestation (later preterm)? e. Multiple gestation?							

f. Racial or ethnic subgroups? g. Women with previous preterm birth? h. Women with history of preeclampsia? i. Women with RPTL and women without RPTL?							
Studies reported surrogate outcomes of preterm labor much more frequently than neonatal or maternal clinical endpoints. However, none of the included studies examined incidence of delivery < 28 weeks (strength of evidence is insufficient, Table B), need for oxygen per nasal cannula, or ratio of birth weight/gestational age at delivery. **Incidence of Delivery at Various Gestational Ages** Incidence of delivery < 32 weeks: The strength of evidence favoring SQ terbutaline pump compared with either oral tocolytics or no treatment is low for women with RPTL and those additionally with twin gestation (OR range = 0.04–0.52, 95% CI range: 0.00–0.35, 0.50–0.76) (Table B). The evidence originated in six, mostly Matria-based, cohort studies of medium to high risk of bias.13,15-19 Incidence of delivery < 34 weeks: The strength of evidence for this outcome is insufficient (Table B). One small RCT (n=52) that did not	**Cycle 2 (December 2012)**					**Up-to-date**	**Up-to-date**
	No new eligible evidence was identified	**None**	**None**	No new saftey alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		
	Cycle 1 (May 2012)						
	No new eligible evidence was identified	**None**	**None**	No new saftey alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings. However, one expert had the following comment during the first		

address any of the populations of interest, showed a nonsignificant difference between SQ terbutaline pump and placebo in women with singleton gestation.10 Incidence of delivery < 37 weeks: The strength of evidence favoring SQ terbutaline pump compared with oral tocolytics or no treatment is insufficient or low for women with RPTL (Table B). Four of five cohort studies of medium to high risk of bias, mostly from the Matria database, reported statistically significant differences in favor of SQ terbutaline pump (OR range= 0.04–0.75, 95% CI range: 0.01–0.58, 0.23–1.20).13,15,17,18,20 **Mean Gestational age at Delivery** Larger cohort studies of medium to high risk of bias in women with RPTL and single or twin gestation demonstrated consistent benefit of SQ terbutaline pump compared with oral tocolytics or no treatment (RPTL and singleton gestation: difference in means range = 0.70–3.40 weeks, 95% CI range: 0.28–1.80 weeks, 0.98–5.00 weeks; RPTL and twin gestation: difference in means = 0.70 weeks, 95% CI range: 0.43–0.48 weeks, 0.92–0.97 weeks).13,15-19 Most participants in the cohort					assessment of this CER: "This assessment understates the risk of bias associated with the studies that are derived from the Matria database. Matria employees are listed as authors. The selection methods are not described or loosely described. The first draft of the study is usually written by the Matria employees and the first author does not have unfettered access to the data. Although the data "favors" SQ terbutaline, it is so highly biased that consideration should be more heavily discounted."		

studies came from the Matria database. RCT evidence not directly addressing the populations of interest yielded a nonsignificant effect estimate between the pump and placebo (n=52 and n=42).10,11 **Prolongation of Pregnancy** The strength of evidence favoring SQ terbutaline pump compared with oral tocolytics or no treatment is insufficient or low for women with twin gestation and/or RPTL (difference in means range 5.50–25.30, 95% CI range: 0.79–16.77, 8.72–33.83) (Table B).13,15-18 This evidence came from five cohort studies of medium to high risk of bias, mostly from the Matria database. Two small RCTs (n=52 and n=42), which did not pertain to any of the populations of interest, showed nonsignificant differences between SQ terbutaline pump and placebo.10,11 In one Matria-based cohort study, more women in the SQ terbutaline pump group had pregnancy prolonged > 7 days compared with women who received oral nifedipine (OR = 7.84, 95% CI: 3.59, 17.12).15 Other Matria-based studies reported statistically significant benefits in favor of the pump compared with oral tocolytics							

for prolongation > 14 days (OR range = 1.93– 3.47, 95% CI range: 0.87–2.34, 2.65–5.15).15-19 **Birth Weight** Cohort studies of women with RPTL and single or twin gestation demonstrated statistically significant differences in mean birth weight in favor of SQ terbutaline pump compared with oral tocolytics or no treatment (range of mean difference in grams = 136–721, 95% CI range: 83–355, 189–1087).13,16-19 Aside from one study, all were from the Matria database.16-19 Two small RCTs (n=52 and n=42), which did not pertain to any of the populations of interest, reported nonsignificant differences between SQ terbutaline pump and placebo.10,11 Incidence of low birth weight (< 2500 g) and very low birth weight (< 1500 g) were reported in cohort studies. Most of these studies originated from the Matria database. All studies that reported low birth weight found statistically significant differences in favor of SQ terbutaline pump compared with no treatment or oral tocolytics (OR range = 0.24–0.64, 95% CI range: 0.06–0.51, 0.62–0.96).13,15-19 Most studies also found statistically							

significant differences in favor of the pump for incidence of very low birth weight (OR range = 0.22-0.46, 95% CI range: 0.07– 0.29, 0.60–1.06).16-19 **Pregnancy Prolongation Index** Pregnancy prolongation index was reported in two cohort studies.13,20 Both found statistically significant differences in favor of the SQ terbutaline pump compared with either no treatment or oral terbutaline (mean difference = 0.41, 95% CI: 0.26, 0.56; and 0.14, 95% CI: 0.02–0.26). **Need for Assisted Ventilation** One cohort study from the Matria database reported a nonsignificant difference between the SQ terbutaline pump and oral tocolytics in requirement for ventilator among infants with NICU admission.18 **NICU Admission** Incidence of NICU Admission: Statistically significant differences in favor of the SQ terbutaline pump compared with oral tocolytics or no treatment were reported in cohort studies of women with RPTL and single or twin gestation (OR range 0.28–0.72, 95% CI range: 0.08– 0.58, 0.63–0.97).13,15-19 Again, most of these studies were Matria-based.15-							

19 One small RCT (n=52), which did not pertain to any of the populations of interest, reported a nonsignificant difference between the SQ terbutaline pump and placebo.10 NICU length of stay: Statistically significant differences in favor of the SQ terbutaline pump compared with oral tocolytics or no treatment were also reported for NICU length of stay in mostly Matria-based cohort studies of women with RPTL and single or twin gestation (range of mean difference in days: -3.50 to -17.90, 95% CI range: -5.26 to -32.88, -1.74 to 3.54).13,15,18,19 Another small RCT (n=42), which did not address any of the subgroups of interest, reported a nonsignificant difference between the SQ terbutaline pump and placebo or oral terbutaline.11							
Key Question 3: increase the maternal harms of arrhythmia, heart failure, hyperglycemia, hypokalemia, maternal mortality, myocardial infarction, pulmonary edema, or refractory hypotension, or result in an increased rate of maternal discontinuation of therapy or maternal withdrawal due to adverse effects (Withdrawal- AE)?							
The strength of evidence is insufficient for Withdrawal-AE (Table B). One prospective cohort in women with singleton gestation and RPTL demonstrated highly unreliable odds favoring no treatment compared with the pump for tachycardia/nervousness	**Cycle 2 (December 2012)**					**Up-to-date**	**Up-to-date**
	No new eligible evidence was identified	**None**	**None**	No new saftey alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence		

(OR=25.48, 95% CI:1.23, 526.6).13 Underpowered studies demonstrated indeterminate results for the outcomes of mortality, pulmonary edema, and therapy discontinuation (i.e., type II error cannot be excluded).10,18,19 Two studies, a retrospective cohort and a nonrandomized trial, demonstrated nonsignificant differences between the SQ terbutaline pump and oral terbutaline in the incidence of gestational diabetes, though type II error cannot be excluded. No data were available on heart failure, myocardial infarction, refractory hypotension, and hypokalemia. Until 2009, 16 maternal deaths and 12 cases of maternal cardiovascular events (hypertension, myocardial infarction tachycardia, arrhythmias, and pulmonary edema) in association with terbutaline tocolysis were reported to the FDA. Of these, at least three maternal deaths and three cardiovascular adverse events were clearly reported to be in association with the use of the SQ terbutaline pump.24					sufficient to invalidate the findings.		
	Cycle 1 (May 2012)						
	No new eligible evidence was identified	**None**	**None**	No new saftey alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		
Key Question 4: increase the neonatal terbutaline-related harms of hypoglycemia, hypocalcemia, and ileus?							
Neonatal harms data were very sparse. Neonatal hypoglycemia was reported in only one RCT that	**Cycle 2 (December 2012)**					**Up-to-date**	**Up-to-date**
	No new eligible	**None**	**None**	No new	Both experts stated that the		

compared the SQ terbutaline pump with placebo and oral terbutaline.11 Differences between the SQ terbutaline pump and placebo or oral terbutaline were nonsignificant. However, given the small number of events and limited sample size (n=42), the RCT was underpowered and the results are inconclusive. No studies reported neonatal hypocalcemia or ileus.	**evidence was identified**			safety alert	conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		
	Cycle 1 (May 2012)						
	No new eligible evidence was identified	**None**	**None**	No new safety alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		
Key Question 5: Can the differences in the outcomes above be partially explained by the differences in level of care (e.g., frequency of followup, nurse visits, concomitant treatment, etc.) and level of activity (e.g., other children in the home, marital/support status, working status, bedrest, etc.) between the terbutaline pump group and the comparator group?							
Only a small number of studies could be rated for level of activity and level of care. Therefore, we could not carry out meta-regressions to explore the effect of these variables on maternal and neonatal outcomes. Furthermore, we	**Cycle 2 (December 2012)**					**Up-to-date**	**Up-to-date**
	No new eligible evidence was identifie	**None**	**None**	No new safety alert	Both experts stated that the conclusion was still valid, and they were not aware of any		

could not even explore the impact of level of activity on effect estimates in a qualitative manner because all studies that could be rated were designated as having "low" level of activity. No apparent trends in effect estimates according to level of care based on qualitative assessments were observed.	**d**				evidence sufficient to invalidate the findings.		
	Cycle 1 (May 2012)						
	No new eligible evidence was identified	**None**	**None**	No new safety alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		
Key Question 6: What is the incidence of failure of the pump device used for terbutaline infusion, including missed doses, dislodgment, and overdose?							
Two case series and one RCT reported outcomes related to the pump device.11,22,23 In a case series of 51 women, one participant had dislodgment of catheter (2 percent, exact central CI: 0.5%, 10%) and there was one pump that malfunctioned (2 percent, exact central CI: 0.5%, 10%).22 No infusion site infections or mechanical failures were observed in a case series of nine women.23 An underpowered	**Cycle 2 (December 2012)**					**Up-to-date**	**Up-to-date**
	No new eligible evidence was identified	**None**	**None**	No new saftey alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		

RCT demonstrated indeterminate results for the outcomes of local pain and local skin irritation.11 No data were available for missed doses or overdoses.	**Cycle 1 (May 2012)**						
	No new eligible evidence was identified	**None**	**None**	No new saftey alert	Both experts stated that the conclusion was still valid, and they were not aware of any evidence sufficient to invalidate the findings.		
CER=comparative effectiveness review; FDA=food and drug administration; vs.: versus; MD: mean difference; NR: Not Reported							

Reference List

1. Gaudet LM, Singh K, Weeks L, et al. Effectiveness of terbutaline pump for the prevention of preterm birth. A systematic review and meta-analysis. PLoS One 2012;7(2):e31679 . [PMID: PM:22363704].

2. Shekelle P, Newberry S, Maglione M et al. Assessment of the need to update comparative effectiveness reviews: Report of an initial rapid program assessment (2005-2009) [Internet]. 2009 Sep 10.

3. Shekelle PG, Newberry SJ, Wu H et al. Identifying signals for updating systematic reviews: A comparison of two methods [Internet]. 2011 Jun.

4. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007 Aug 21;147(4):224-33. [PMID: PM:17638714].

5. Porat S, Amsalem H, Shah PS et al. Transabdominal amnioinfusion for preterm premature rupture of membranes: A systematic review ar metaanalysis of randomized and observational studies. 207. Mosb (11830 Westline Industrial Drive, St Louis MO 63146, United States); 20

6. Bricker L, Peden H, Tomlinson AJ et Titrated low-dose vaginal and/or or misoprostol to induce labour for prelabour membrane rupture: A randomised trial. 115. Blackwell Publishing Ltd (9600 Garsington Roa Oxford OX4 2XG, United Kingdom); 12.

7. Conde-Agudelo A, Romero R, Kusan JP. Nifedipine in the management o preterm labor: A systematic review metaanalysis. 204. Mosby Inc. (11 Westline Industrial Drive, St. Louis M 63146, United States); 2011. 2.

8. Usta IM, Khalil A, Nassar AH. Oxyto antagonists for the management of preterm birth: A review. Am J Perin 2011;28(6):449-59.

Source: www.effectivehealthcare.ahrq.gov
Published online: January 30, 2013

Appendix A: Search Methodology

All MEDLINE and Embase searches were limited to the following journals:

General biomedical – Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine

Specialty journals – Am J Obstet Gynecol, Am J Perinatol, Int J Gynaecol Obstet, Obstet Gynecol, and BJOG

Main Search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:
---
1 exp Obstetric Labor, Premature/ (16342)
2 (PTL or PTB or RPTL).ti,ab. (3184)
3 ((premature* or pre-mature* or preterm or pre-term or early) adj5 (labor* or labour* or birth* or deliver*)).ti,ab. (36719)
4 ((premature* or pre-mature* or preterm or pre-term or early) adj5 ((uterine or uterus) adj2 contract*)).ti,ab. (316)
5 Tocolysis/ or Tocolytic Agents/ (1966)
6 (tocolysis or tocolytic*).ti,ab. (2832)
7 1 or 2 or 3 or 4 or 5 or 6 (45730)
8 exp Terbutaline/ (2924)
9 (Terbutalin* or Brethaire or Brethine or Bricanyl or "BRN 2370513" or "EINECS 245-385-8" or "UNII-N8ONU3L3PG").ti,ab. (3106)
10 (23031 25 6 terbutaline or 23031 32 5 terbutaline sulfate).rn. (2924)
11 8 or 9 or 10 (3777)
12 exp Injections, Subcutaneous/ (33775)
13 exp Infusion Pumps/ (10857)
14 exp Home Infusion Therapy/ (578)
15 exp Infusions, Parenteral/ (79311)
16 (subcutaneous* or SubQ or sub-cutaneous* or pump or pumps or infuse or infused or infuses or infusing or infusion* or infuser*).ti,ab. (389343)
17 ((home adj3 therapy) or (home adj3 therapies) or (home adj3 tocoyl*) or (home-based adj3 therapy) or (home-based adj3 therapies) or (home-based adj3 tocoyl*)).ti,ab. (2577)
18 ((maintenance adj3 therapy) or (maintenance adj3 therapies) or (maintenance adj3 therapeutic) or (maintenance adj3 treatment*) or (maintenance adj3 tocoly*) or (supportive adj3 therapy) or (supportive adj3 therapies) or (supportive adj3 treatment*) or (supportive adj3 tocoyls*) or (outpatient adj3 therapy) or (outpatient adj3 therapies) or (outpatient* adj3 treatment*) or (outpatient* adj3 tocoly*)).ti,ab. (31989)
19 ((long-term adj therapy) or (long-term adj therapies) or (long-term adj therapeutic) or (long-term adj treatment*) or (long-term adj management) or (long-term adj tocoly*) or (longterm adj therapy) or (longterm adj therapies) or (longterm adj therapeutic) or (longterm adj treatment*) or (longterm adj management) or (longterm adj tocoly*)).ti,ab. (25796)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (502147)
21 11 and 20 (686)
22 7 and 21 (144)
23 ("annals of internal medicine" or bmj or jama or lancet or "new england journal of medicine").jn. (355161)
24 "american journal of obstetrics & gynecology".jn. (35250)

25 "american journal of perinatology".jn. (2896)
26 "international journal of gynaecology & obstetrics".jn. (7619)
27 obstetrics & gynecology.jn. (23124)
28 "bjog an international journal of obstetrics & gynaecology".jn. (3857)
29 or/23-28 (427907)
30 22 and 29 (65)
31 (201010* or 201911* or 201012* or 2011* or 2012*).ed. (2141186)
32 30 and 31 (0)

****

Database: Embase <1980 to 2012 Week 44>
Search Strategy:
---
1 exp premature labor/ (23915)
2 (PTL or PTB or RPTL).ti,ab. (4031)
3 ((Premature* or pre-mature* or preterm or pre-term or early) adj5 (labor* or labour* or birth* or deliver*)).ti,ab. (45185)
4 ((Premature* or pre-mature* or preterm or pre-term or early) adj5 ((uterine or uterus) adj2 contract*)).ti,ab. (380)
5 exp Tocolysis/ (2785)
6 (tocolysis or tocolytic*).ti,ab. (3586)
7 1 or 2 or 3 or 4 or 5 or 6 (57067)
8 exp terbutaline/ (9618)
9 exp terbutaline sulfate/ (569)
10 (23031 25 6 or 23031 32 5).rn. (9905)
11 (Terbutalin* or Brethaire or Brethine or Bricanyl or "BRN 2370513" or "EINECS 245-385-8" or "UNII-N8ONU3L3PG").ti,ab. (3528)
12 (Terbutalin* or Brethaire or Brethine or Bricanyl).tn. (1462)
13 8 or 9 or 11 or 12 (10357)
14 exp subcutaneous drug administration/ (83132)
15 exp infusion pump/ (5698)
16 exp infusion/ (66482)
17 (subcutaneous* or SubQ or sub-cutaneous* or pump or pumps or infuse or infused or infuses or infusing or infusion* or infuser*).ti,ab. (451870)
18 ((home adj3 therapy) or (home adj3 therapies) or (home adj3 tocoyl*) or (home-based adj3 therapy) or (home-based adj3 therapies) or (home-based adj3 tocoyl*)).ti,ab. (3242)
19 ((maintenance adj3 therapy) or (maintenance adj3 therapies) or (maintenance adj3 therapeutic) or (maintenance adj3 treatment*) or (maintenance adj3 tocoly*) or (supportive adj3 therapy) or (supportive adj3 therapies) or (supportive adj3 treatment*) or (supportive adj3 tocoyls*) or (outpatient adj3 therapy) or (outpatient adj3 therapies) or (outpatient* adj3 treatment*) or (outpatient* adj3 tocoly*)).ti,ab. (42045)
20 ((long-term adj therapy) or (long-term adj therapies) or (long-term adj therapeutic) or (long-term adj treatment*) or (long-term adj management) or (long-term adj tocoly*) or (longterm adj therapy) or (longterm adj therapies) or (longterm adj therapeutic) or (longterm adj treatment*) or (longterm adj management) or (longterm adj tocoly*)).ti,ab. (33280)
21 14 or 15 or 16 or 17 or 18 or 19 or 20 (609050)

22 13 and 21 (1390)
23 7 and 22 (229)
24 lancet.jn. (117674)
25 ("jama journal of the american medical association" or "jama the journal of the american medical association").jn. (43005)
26 "annals of internal medicine".jn. (29641)
27 (bmj or bmj clinical research ed).jn. (35898)
28 "new england journal of medicine".jn. (38089)
29 "american journal of obstetrics and gynecology".jn. (34831)
30 "american journal of perinatology".jn. (2972)
31 "international journal of gynaecology and obstetrics the official organ of the international federation of gynaecology and obstetrics".jn. (557)
32 "obstetrics and gynecology".jn. (22902)
33 "bjog an international journal of obstetrics and gynaecology".jn. (5120)
34 or/24-33 (330689)
35 23 and 34 (80)
36 (2011* or 2012*).em. (2172094)
37 35 and 36 (3)

****

Cochrane Library 2012 Issue 3

ID Search Hits
#1 MeSH descriptor: [Obstetric Labor, Premature] explode all trees 939
#2 PTL or PTB or RPTL:ti,ab,kw 70
#3 (premature* near/5 labor*) or (premature* near/5 labour*) or (premature* near/5 birth*) or (premature* near/5 deliver*) or (premature* near/5 uterine next contraction*):ti,ab,kw OR (preterm near/5 labor*) or (preterm near/5 labour*) or (preterm near/5 birth*) or (preterm near/5 deliver*) or (preterm near/5 uterine next contraction*):ti,ab,kw OR (pre next mature* near/5 labor*) or (pre next mature* near/5 labour*) or (pre next mature* near/5 birth*) or (pre next mature* near/5 deliver*) or (pre next mature* near/5 uterine next contraction*):ti,ab,kw OR (pre next term near/5 labor*) or (pre next term near/5 labour*) or (pre next term near/5 birth*) or (pre next term near/5 deliver*) or (pre next term near/5 uterine next contraction*):ti,ab,kw 2935
#4 #1 or #2 or #3 2978
#5 MeSH descriptor: [Terbutaline] explode all trees 708
#6 Terbutalin* or Brethaire or Brethine or Bricanyl or "BRN 2370513" or "EINECS 245-385-8" or "UNII-N8ONU3L3PG":ti,ab,kw 1271
#7 #5 or #6 1271
#8 MeSH descriptor: [Injections, Subcutaneous] explode all trees 3246
#9 MeSH descriptor: [Infusion Pumps] explode all trees 900
#10 MeSH descriptor: [Home Infusion Therapy] explode all trees 24
#11 MeSH descriptor: [Infusions, Parenteral] explode all trees 10221
#12 subcutaneous* or SubQ or sub next cutaneous* or pump or pumps:ti,ab,kw 13978
#13 continuous next infusion*:ti,ab,kw 3170
#14 (home next infusion* or maintenance next tocoly* or maintenance next therapy or maintenance next treatment or supportive next therapy or outpatient next therapy or outpatient next treatment):ti,ab,kw 4539
#15 #8 or #9 or #10 or #11 or #12 or #13 or #14 30309

#16 #7 and #15 180
#17 #4 and #16 from 2011 to 2012 4

DSR – 1
DARE – 1
HTA – 2

No hits meet inclusion criteria

****
CINAHL
Friday, November 09, 2012 9:02:36 AM

#	Query	Limiters/Expanders	Results
S28	S19 and S26	Limiters - Published Date from: 20110901-20121131 Expanders - Apply related words Search modes - Boolean/Phrase	0
S27	S19 and S26	Expanders - Apply related words Search modes - Boolean/Phrase	33
S26	S20 or S21 or S22 or S23 or S24 or S25	Expanders - Apply related words Search modes - Boolean/Phrase	38,674
S25	TX ((long-term W1 therapy) or (long-term W1 therapies) or (long-term W1 therapeutic) or (long-term W1 treatment*) or (long-term W1 management) or (long-term W1 tocoly*) or (longterm W1 therapy) or (longterm W1 therapies) or (longterm W1 therapeutic) or (longterm W1 treatment*) or (longterm W1 management) or (longterm W1 tocoly*))	Expanders - Apply related words Search modes - Boolean/Phrase	5,025
S24	TX ((maintenance N3 therapy) or (maintenance N3 therapies) or (maintenance N3 therapeutic) or (maintenance N3 treatment*) or (maintenance N3 tocoyl*) or (supportive N3 therapy) or (supportive N3 therapies) or (supportive N3 treatment*) or (supportive N3 tocoly*) or (outpatient* N3 therapy) or (outpatient* N3 therapies) or (outpatient* N3 therapeutic) or (outpatient* N3 treatment*) or (outpatient* N3 tocoyl*))	Expanders - Apply related words Search modes - Boolean/Phrase	5,559
S23	TX ((home N3 therapy) or (home N3 therapies) or (home N3 tocoly*) or (home-based N3 therapy) or (home-based N3 therapies) or (home-based N3 tocoly*))	Expanders - Apply related words Search modes - Boolean/Phrase	2,868
S22	TX subcutaneous* or SubQ or sub-cutaneous* or pump or pumps or infuse or infused or infuses or infusing or infusion* or infuser	Expanders - Apply related words Search modes - Boolean/Phrase	26,373

S21	(MH "Infusions, Parenteral+")	Expanders - Apply related words Search modes - Boolean/Phrase	5,717
S20	(MH "Injections, Subcutaneous+")	Expanders - Apply related words Search modes - Boolean/Phrase	1,638
S19	s15 AND s18	Expanders - Apply related words Search modes - Boolean/Phrase	72
S18	S16 or S17	Expanders - Apply related words Search modes - Boolean/Phrase	237
S17	TX Terbutalin* or Brethaire or Brethine or Bricanyl or "BRN 2370513" or "EINECS 245- 385-8" or "UNII-N8ONU3L3PG"	Expanders - Apply related words Search modes - Boolean/Phrase	237
S16	(MH "Terbutaline")	Expanders - Apply related words Search modes - Boolean/Phrase	160
S15	S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14	Expanders - Apply related words Search modes - Boolean/Phrase	7,923
S14	TX Tocolytic OR tocolysis	Expanders - Apply related words Search modes - Boolean/Phrase	513
S13	TX (pre-term N5 (uterus N2 contract*))	Expanders - Apply related words Search modes - Boolean/Phrase	0
S12	TX (preterm N5 (uterus N2 contract*))	Expanders - Apply related words Search modes - Boolean/Phrase	0
S11	TX (premature* N5 (uterus N2 contract*))	Expanders - Apply related words Search modes - Boolean/Phrase	1
S10	TX (early N5 (uterine N2 contract*))	Expanders - Apply related words Search modes - Boolean/Phrase	5
S9	TX (pre-term N5 (uterine N2 contract*))	Expanders - Apply related words Search modes - Boolean/Phrase	0
S8	TX (preterm N5 (uterine N2 contract*))	Expanders - Apply related words Search modes - Boolean/Phrase	34
S7	TX (pre-mature* N5 (uterine N2 contract*))	Expanders - Apply related words	0

		Search modes - Boolean/Phrase	
S6	TX (premature* N5 (uterine N2 contract*))	Expanders - Apply related words Search modes - Boolean/Phrase	5
S5	TX (early N5 labor*) OR (early N5 labour*) OR (early N5 birth*) OR (early N5 deliver*)	Expanders - Apply related words Search modes - Boolean/Phrase	1,508
S4	TX ((preterm N5 labor*) or (preterm n5 labour*) or (preterm n5 birth*) or (preterm n5 deliver*)) or TX ((pre-term N5 labor*) or (pre-term n5 labour*) or (pre-term n5 birth*) or (pre-term n5 deliver*))	Expanders - Apply related words Search modes - Boolean/Phrase	4,844
S3	TX ((premature* N5 labor*) or (premature* n5 labour*) or (premature* n5 birth*) or (premature* n5 deliver*)) or TX ((pre-mature* N5 labor*) or (pre-mature* n5 labour*) or (pre-mature* n5 birth*) or (pre-mature* n5 deliver*))	Expanders - Apply related words Search modes - Boolean/Phrase	2,978
S2	TX PTL or PTB or RPTL	Expanders - Apply related words Search modes - Boolean/Phrase	276
S1	(MH "Labor, Premature")	Expanders - Apply related words Search modes - Boolean/Phrase	1,890

****

CRD Search Update – 2012 Nov 9

Set	Query	
1	MeSH DESCRIPTOR Obstetric Labor, Premature EXPLODE ALL TREES	
2	PTL OR PTB OR RPT	12
3	(premature* NEAR labor*) OR (premature* NEAR labour*) OR (premature* NEAR birth*) OR (premature* NEAR deliver*)	192
4	(premature NEAR contract*)	8
5	(pre NEAR mature* NEAR labor*) OR (pre NEAR mature* NEAR labour*) OR (pre NEAR mature* NEAR birth*) OR (pre NEAR mature* NEAR deliver*)	1
6	pre NEAR mature NEAR contract*	0
7	(preterm NEAR labor*) OR (preterm NEAR labour*) OR (preterm NEAR birth*) OR (preterm NEAR deliver*)	443
8	preterm NEAR contract*	14
9	(pre NEAR term NEAR labor*) OR (pre NEAR term NEAR labour*) OR (pre NEAR term NEAR birth*) OR (pre NEAR term NEAR deliver*)	117
10	(pre NEAR term NEAR contract*)	0
11	(early NEAR labor*) OR (early NEAR labour*) OR (early NEAR birth*) OR (early NEAR deliver*)	99
12	early NEAR contract*	5
13	MeSH DESCRIPTOR Tocolysis EXPLODE ALL TREES	12
14	tocolysis OR tocolytic*	92

15	MeSH DESCRIPTOR Terbutaline EXPLODE ALL TREES	21
16	Terbutalin* OR Brethaire OR Brethine OR Bricanyl OR "BRN 2370513" OR "EINECS 245-385-8" OR "UNII-N8ONU3L3PG"	55
17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	656
18	#15 OR #16	55
19	#17 AND #18	23
20	MeSH DESCRIPTOR Injections, Subcutaneous EXPLODE ALL TREES	97
21	MeSH DESCRIPTOR Infusion Pumps EXPLODE ALL TREES	89
22	MeSH DESCRIPTOR Home Infusion Therapy EXPLODE ALL TREES	8
23	MeSH DESCRIPTOR Infusions, Parenteral EXPLODE ALL TREES	323
24	subcutaneous* OR SubQ OR (sub NEAR cutaneous*) OR pump OR 2070 A-7 pumps OR infuse OR infused OR infuses OR infusing OR infusion* OR infuser*	2184
25	(home NEAR therapy) OR (home NEAR therapies) OR (home NEAR tocoyl*)	146
26	(maintenance NEAR therapy) or (maintenance NEAR therapies) or (maintenance NEAR therapeutic) or (maintenance NEAR treatment*) or (maintenance NEAR tocoly*) or (supportive NEAR therapy) or (supportive NEAR therapies) or (supportive NEAR treatment*) or (supportive NEAR tocoyls*) or (outpatient NEAR therapy) or (outpatient NEAR therapies) or (outpatient* NEAR treatment*) or (outpatient* NEAR tocoly*)	1408
27	(maintenance NEAR therapy) OR (maintenance NEAR therapies) OR (maintenance NEAR therapeutic) OR (maintenance NEAR treatment*) OR (maintenance NEAR tocoly*)	720
28	(supportive NEAR therapy) OR (supportive NEAR therapies) OR (supportive NEAR treatment*) OR (supportive NEAR tocoyls*)	260
29	(outpatient NEAR therapy) OR (outpatient NEAR therapies) OR (outpatient* NEAR treatment*) OR (outpatient* NEAR tocoly*)	471
30	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	3580
31	#19 AND #30	18
32	(#31) WHERE PD FROM 30/09/2011 TO 09/11/2012	6

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of "opposing findings" – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details
**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B: Updating Signals (Continued)

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the 'borderline' changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old <=0.5 or RRR new / RRR old >=1.5. Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old <=0.5 or RD new / RD old >=1.5).

* Please, see Shojania et al. 2007 for further definitions and details

Appendix C: Evidence Table (Terbutaline)

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
Key Question 1: improve neonatal health outcomes, including bronchopulmonary dysplasia, neonatal death, death within initial hospitalization, significant intraventricular hemorrhage (grade III/IV), necrotizing enterocolitis, periventricular leukomalacia, retinopathy of prematurity, seizures, sepsis, and stillbirth for the following subgroups: a. Women <28 weeks of gestation (extremely preterm)? b. Women between 28 weeks and 31 weeks of gestation (very preterm)? c. Women between 32 weeks and 33 weeks of gestation (preterm)? d. Women between 34 weeks and 36 weeks of gestation (later preterm)? e. Multiple gestations? f. Racial or ethnic subgroups? g. Women with previous preterm birth? h. Women with history of preeclampsia? i. Women with RPTL and women without RPTL?						
Assessment 2 (December 2012)						
No eligible publication was identified.						
Assessment 1 (May 2012)						
No eligible publication was identified.						
Key Question 2: improve other surrogate outcomes, including gestational age at delivery, incidence of delivery at various gestational ages (<28 weeks, < 32 weeks, <34 weeks, <37 weeks), mean prolongation of pregnancy (days), birth weight, ratio of birth weight/gestational age at delivery, pregnancy prolongation index, need for assisted ventilation, need for oxygen per nasal cannula, and neonatal intensive care unit (NICU) admission for the following subgroups:						

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
b. Women between 28 weeks and 31 weeks of gestation (very preterm)? c. Women between 32 weeks and 33 weeks of gestation (preterm)? d. Women between 34 weeks and 36 weeks of gestation (later preterm)? e. Multiple gestation? f. Racial or ethnic subgroups? g. Women with previous preterm birth? h. Women with history of preeclampsia? i. Women with RPTL and women without RPTL?						
Assessment 2 (December 2012)						
No eligible publication was identified.						
Assessment 1 (May 2012)						
No eligible publication was identified.						
Key Question 3: increase the maternal harms of arrhythmia, heart failure, hyperglycemia, hypokalemia, maternal mortality, myocardial infarction, pulmonary edema, or refractory hypotension, or result in an increased rate of maternal discontinuation of therapy or maternal withdrawal due to adverse effects (Withdrawal- AE)?						
Assessment 2 (December 2012)						
No eligible publication was identified.						
Assessment 1 (May 2012)						
No eligible publication was identified.						
Key Question 4: increase the neonatal terbutaline-related harms of hypoglycemia, hypocalcemia, and ileus?						
Assessment 2 (December 2012)						
No eligible publication was identified.						

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
Assessment 1 (May 2012)						
No eligible publication was identified.						
Key Question 5: Can the differences in the outcomes above be partially explained by the differences in level of care (e.g., frequency of followup, nurse visits, concomitant treatment, etc.) and level of activity (e.g., other children in the home, marital/support status, working status, bedrest, etc.) between the terbutaline pump group and the comparator group?						
Assessment 2 (December 2012)						
No eligible publication was identified.						
Assessment 1 (May 2012)						
No eligible publication was identified.						
Key Question 6: What is the incidence of failure of the pump device used for terbutaline infusion, including missed doses, dislodgment, and overdose?						
Assessment 2 (December 2012)						
No eligible publication was identified.						
Assessment 1 (May 2012)						
No eligible publication was identified.						

Appendix D: Questionnaire Matrix (Terbutaline)

Comparative Effectiveness of Terbutaline Pump for the Prevention of Preterm Birth

AHRQ Publication No. HHSA 290 2007 10059 I September 2011

Access to full report: http://www.effectivehealthcare.ahrq.gov/ehc/products/157/783/Terbutaline_CER_20111229.pdf

Clinical expert name:

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 1: improve neonatal health outcomes, including bronchopulmonary dysplasia, neonatal death, death within initial hospitalization, significant intraventricular hemorrhage (grade III/IV), necrotizing enterocolitis, periventricular leukomalacia, retinopathy of prematurity, seizures, sepsis, and stillbirth for the following subgroups: a. Women <28 weeks of gestation (extremely preterm)? b. Women between 28 weeks and 31 weeks of gestation (very preterm)? c. Women between 32 weeks and 33 weeks of gestation (preterm)? d. Women between 34 weeks and 36 weeks of gestation (later preterm)? e. Multiple gestations? f. Racial or ethnic subgroups? g. Women with previous preterm birth? h. Women with history of preeclampsia? i. Women with RPTL and women without RPTL?			
Strength of evidence is insufficient for bronchopulmonary dysplasia, death within initial hospitalization, and significant intraventricular hemorrhage (grade III/IV). Based on one retrospective cohort of medium risk of bias, the strength of evidence favoring the SQ terbutaline pump compared with oral tocolytics for neonatal death in women with twin gestation and RPTL is low (Table B). This study investigated women from the Matria database and reported a statistically significant difference in neonatal death in favor			

of SQ terbutaline pump (OR = 0.09, 95% CI: 0.01, 0.70).19 Sparse evidence from underpowered studies addressed necrotizing enterocolitis, retinopathy of prematurity, and sepsis with inconclusive results.11,13 No data were available for periventricular leukomalacia and seizures. Three retrospective cohort studies from the Matria database reported stillbirths in women with RPTL and single or twin gestation.17-19 All three studies found nonsignificant differences between the SQ terbutaline pump and oral tocolytics. However, these studies were likely underpowered to detect a difference in still birth, given the small number of events (<1%).			
Key Question 2: improve other surrogate outcomes, including gestational age at delivery, incidence of delivery at various gestational ages (<28 weeks, < 32 weeks, <34 weeks, <37 weeks), mean prolongation of pregnancy (days), birth weight, ratio of birth weight/gestational age at delivery, pregnancy prolongation index, need for assisted ventilation, need for oxygen per nasal cannula, and neonatal intensive care unit (NICU) admission for the following subgroups: a. Women <28 weeks of gestation (extremely preterm)? b. Women between 28 weeks and 31 weeks of gestation (very preterm)? c. Women between 32 weeks and 33 weeks of gestation (preterm)? d. Women between 34 weeks and 36 weeks of gestation (later preterm)? e. Multiple gestation? f. Racial or ethnic subgroups? g. Women with previous preterm birth? h. Women with history of preeclampsia? i. Women with RPTL and women without RPTL?			
Studies reported surrogate outcomes of preterm labor much more frequently than neonatal or maternal clinical endpoints. However, none of the included studies examined incidence of delivery < 28 weeks (strength of evidence is insufficient, Table B), need for oxygen per nasal cannula, or ratio of birth weight/gestational age at delivery. **Incidence of Delivery at Various Gestational Ages** Incidence of delivery < 32 weeks: The strength of evidence favoring SQ terbutaline pump compared with either oral tocolytics or no treatment is low for women with RPTL and those additionally with twin gestation (OR range = 0.04–0.52, 95% CI range: 0.00–0.35, 0.50–0.76) (Table B). The evidence originated in six, mostly Matria-based, cohort studies of medium to high risk of bias.13,15-19 Incidence of delivery < 34 weeks: The strength of evidence for this outcome is insufficient			

(Table B). One small RCT (n=52) that did not address any of the populations of interest, showed a nonsignificant difference between SQ terbutaline pump and placebo in women with singleton gestation.10 Incidence of delivery < 37 weeks: The strength of evidence favoring SQ terbutaline pump compared with oral tocolytics or no treatment is insufficient or low for women with RPTL (Table B). Four of five cohort studies of medium to high risk of bias, mostly from the Matria database, reported statistically significant differences in favor of SQ terbutaline pump (OR range= 0.04–0.75, 95% CI range: 0.01–0.58, 0.23 1.20).13,15,17,18,20 **Mean Gestational age at Delivery** Larger cohort studies of medium to high risk of bias in women with RPTL and single or twin gestation demonstrated consistent benefit of SQ terbutaline pump compared with oral tocolytics or no treatment (RPTL and singleton gestation: difference in means range = 0.70–3.40 weeks, 95% CI range: 0.28–1.80 weeks, 0.98–5.00 weeks; RPTL and twin gestation: difference in means = 0.70 weeks, 95% CI range: 0.43–0.48 weeks, 0.92–0.97 weeks).13,15-19 Most participants in the cohort studies came from the Matria database. RCT evidence not directly addressing the populations of interest yielded a nonsignificant effect estimate between the pump and placebo (n=52 and n=42).10,11 **Prolongation of Pregnancy** The strength of evidence favoring SQ terbutaline pump compared with oral tocolytics or no treatment is insufficient or low for women with twin gestation and/or RPTL (difference in means range 5.50–25.30, 95% CI range: 0.79–16.77, 8.72–33.83) (Table B).13,15-18 This evidence came from five cohort studies of medium to high risk of bias, mostly from the Matria database. Two small RCTs (n=52 and n=42), which did not pertain to any of the populations of interest, showed nonsignificant differences between SQ terbutaline pump and placebo.10,11 In one Matria-based cohort study, more women in the SQ terbutaline pump group had pregnancy prolonged > 7 days compared with women who received oral nifedipine (OR =			

7.84, 95% CI: 3.59, 17.12).15 Other Matria-based studies reported statistically significant benefits in favor of the pump compared with oral tocolytics for prolongation > 14 days (OR range = 1.93–3.47, 95% CI range: 0.87–2.34, 2.65–5.15).15-19 **Birth Weight** Cohort studies of women with RPTL and single or twin gestation demonstrated statistically significant differences in mean birth weight in favor of SQ terbutaline pump compared with oral tocolytics or no treatment (range of mean difference in grams = 136–721, 95% CI range: 83–355, 189–1087).13,16-19 Aside from one study, all were from the Matria database.16-19 Two small RCTs (n=52 and n=42), which did not pertain to any of the populations of interest, reported nonsignificant differences between SQ terbutaline pump and placebo.10,11 Incidence of low birth weight (< 2500 g) and very low birth weight (< 1500 g) were reported in cohort studies. Most of these studies originated from the Matria database. All studies that reported low birth weight found statistically significant differences in favor of SQ terbutaline pump compared with no treatment or oral tocolytics (OR range = 0.24–0.64, 95% CI range: 0.06–0.51, 0.62–0.96).13,15-19 Most studies also found statistically significant differences in favor of the pump for incidence of very low birth weight (OR range = 0.22-0.46, 95% CI range: 0.07– 0.29, 0.60–1.06).16-19 **Pregnancy Prolongation Index** Pregnancy prolongation index was reported in two cohort studies.13,20 Both found statistically significant differences in favor of the SQ terbutaline pump compared with either no treatment or oral terbutaline (mean difference = 0.41, 95% CI: 0.26, 0.56; and 0.14, 95% CI: 0.02–0.26). **Need for Assisted Ventilation** One cohort study from the Matria database reported a nonsignificant difference between the SQ terbutaline pump and oral tocolytics in requirement for ventilator among infants with NICU admission.18 **NICU Admission** Incidence of NICU Admission: Statistically significant			

differences in favor of the SQ terbutaline pump compared with oral tocolytics or no treatment were reported in cohort studies of women with RPTL and single or twin gestation (OR range 0.28–0.72, 95% CI range: 0.08– 0.58, 0.63–0.97).13,15-19 Again, most of these studies were Matria-based.15-19 One small RCT (n=52), which did not pertain to any of the populations of interest, reported a nonsignificant difference between the SQ terbutaline pump and placebo.10 NICU length of stay: Statistically significant differences in favor of the SQ terbutaline pump compared with oral tocolytics or no treatment were also reported for NICU length of stay in mostly Matria-based cohort studies of women with RPTL and single or twin gestation (range of mean difference in days: -3.50 to -17.90, 95% CI range: -5.26 to -32.88, -1.74 to -3.54).13,15,18,19 Another small RCT (n=42), which did not address any of the subgroups of interest, reported a nonsignificant difference between the SQ terbutaline pump and placebo or oral terbutaline.11			
Key Question 3: increase the maternal harms of arrhythmia, heart failure, hyperglycemia, hypokalemia, maternal mortality, myocardial infarction, pulmonary edema, or refractory hypotension, or result in an increased rate of maternal discontinuation of therapy or maternal withdrawal due to adverse effects (Withdrawal- AE)?			
The strength of evidence is insufficient for Withdrawal-AE (Table B). One prospective cohort in women with singleton gestation and RPTL demonstrated highly unreliable odds favoring no treatment compared with the pump for tachycardia/nervousness (OR=25.48, 95% CI:1.23, 526.6).13 Underpowered studies demonstrated indeterminate results for the outcomes of mortality, pulmonary edema, and therapy discontinuation (i.e., type II error cannot be excluded).10,18,19 Two studies, a retrospective cohort and a nonrandomized trial, demonstrated nonsignificant differences between the SQ terbutaline pump and oral terbutaline in the incidence of gestational diabetes, though type II error cannot be excluded. No data were available on heart failure, myocardial infarction, refractory hypotension, and hypokalemia. Until 2009, 16 maternal deaths and 12 cases of maternal cardiovascular events (hypertension, myocardial infarction tachycardia, arrhythmias, and pulmonary edema) in association with terbutaline tocolysis were reported to the			

FDA. Of these, at least three maternal deaths and three cardiovascular adverse events were clearly reported to be in association with the use of the SQ terbutaline pump.24			
Key Question 4: increase the neonatal terbutaline-related harms of hypoglycemia, hypocalcemia, and ileus?			
Neonatal harms data were very sparse. Neonatal hypoglycemia was reported in only one RCT that compared the SQ terbutaline pump with placebo and oral terbutaline.11 Differences between the SQ terbutaline pump and placebo or oral terbutaline were nonsignificant. However, given the small number of events and limited sample size (n=42), the RCT was underpowered and the results are inconclusive. No studies reported neonatal hypocalcemia or ileus.			
Key Question 5: Can the differences in the outcomes above be partially explained by the differences in level of care (e.g., frequency of followup, nurse visits, concomitant treatment, etc.) and level of activity (e.g., other children in the home, marital/support status, working status, bedrest, etc.) between the terbutaline pump group and the comparator group?			
Only a small number of studies could be rated for level of activity and level of care. Therefore, we could not carry out meta-regressions to explore the effect of these variables on maternal and neonatal outcomes. Furthermore, we could not even explore the impact of level of activity on effect estimates in a qualitative manner because all studies that could be rated were designated as having "low" level of activity. No apparent trends in effect estimates according to level of care based on qualitative assessments were observed.			
Key Question 6: What is the incidence of failure of the pump device used for terbutaline infusion, including missed doses, dislodgment, and overdose?			
Two case series and one RCT reported outcomes related to the pump device.11,22,23 In a case series of 51 women, one participant had dislodgment of catheter (2 percent, exact central CI: 0.5%, 10%) and there was one pump that malfunctioned (2 percent, exact central CI: 0.5%, 10%).22 No infusion site infections or mechanical failures were observed in a case series of nine women.23 An underpowered RCT demonstrated indeterminate results for the outcomes of local pain and local skin irritation.11 No data were available for missed doses or overdoses.			
CER=comparative effectiveness review;			